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ADVANCED OCULAR DRUG DELIVERY SYSTEMS AND EMERGING THERAPEUTICS IN OPHTHALMIC DISEASE MANAGEMENT

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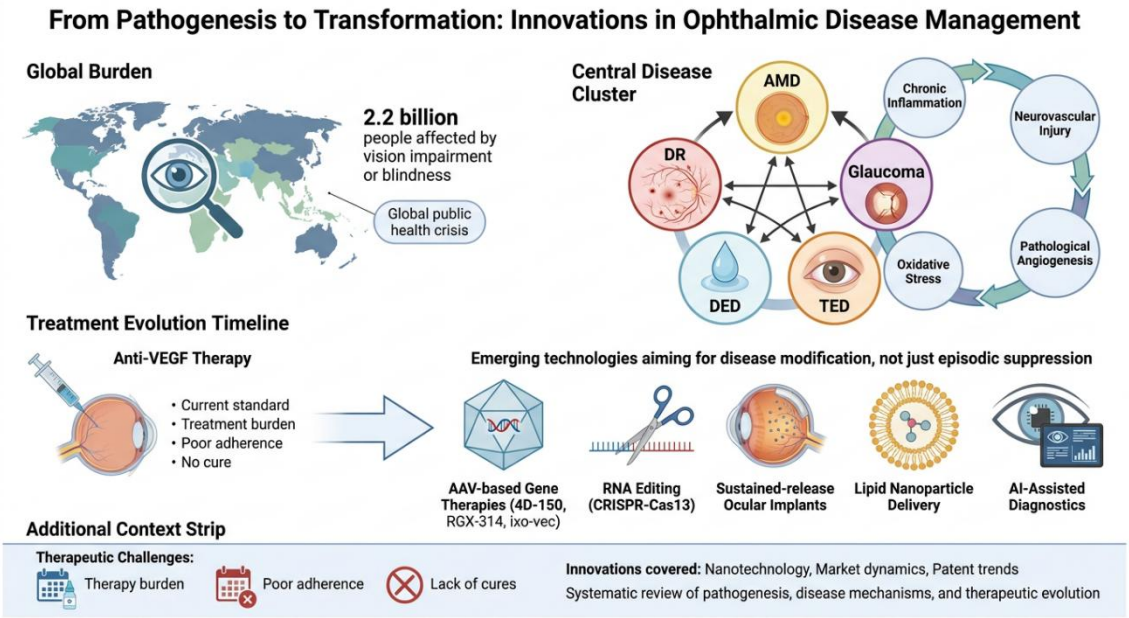
ABSTRACT
Ophthalmic diseases are one of the biggest public health problems, with 2.2 billion people globally having vision impairment or blindness. The key disease groups (age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, dry eye disease (DED) and thyroid eye disease (TED) have common mechanisms of chronic inflammation, neurovascular injury, oxidative stress and pathological angiogenesis. Although the treatment options for anti-VEGF drugs have come a long way in the last 20 years, there remain significant issues such as treatment burden, poor adherence, and the lack of any cure, which restrict the outcomes of treatment. This review covers the pathogenesis, classification, conventional and emerging approaches to the treatment of ophthalmic diseases, nanotechnology based drug delivery, challenges to therapy, recent patent landscape and market dynamics in the field of ophthalmic diseases systematically. We share information on the next generation of transformative technologies, such as AAV-based gene therapies (4D-150, RGX-314, ixo-vec), CRISPR-Cas13 RNA editing, sustained-release ocular implants, lipid nanoparticle delivery platforms and AI-assisted diagnostics, all of which mark a shift from episodic suppression to lasting disease modification.

KEYWORDS – Ophthalmic, Novel ocular drug delivery, Artificial intelligence, Eye disorder, Ophthalmology

Graphical Abstract



Caption: A schematic overview of advanced ocular drug delivery systems and emerging therapeutic strategies for the management of major ophthalmic diseases.

1. INTRODUCTION

Ophthalmology is an ever-changing specialty that involves the diagnosis and treatment of conditions affecting the front and back of the eye [1,2]. Coexisting with progressive potentially blinding conditions such as glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR) and inherited retinal dystrophies are common conditions like refractive errors and dry eye disease [3][4]. In addition to visual impairment, these diseases have a significant impact on functional independence, occupational performance, social participation and psychological health [5].

Worldwide, there are about 2.2 billion people with some degree of visual impairment, including many who have preventable or untreated impairments [6]. DR also impacts almost one-third of all people with diabetes, while

glaucoma affects more than 76 million people throughout the world, and is one of the main causes of permanent vision loss [7][8]. While hundreds of millions of people suffer from dry eye disease, older people are a significant group of people that lose their central vision due to AMD.

Despite the high prevalence of ophthalmic disease, ophthalmic therapeutics are undergoing dramatic changes in technology [10]. There has been an increase in the number of new therapeutic options, including retinal gene therapy, complement inhibitors, sustained-release drugs, nanotechnology, RNA-based therapies, regenerative medicine, and artificial intelligence (AI)-assisted imaging [11-13]. This has led to a trend toward more permanent, targeted and possibly disease-modifying treatment in ophthalmology rather than symptomatic treatment [14][15]. This review brings together the latest disease mechanisms, therapeutic strategies, novel technologies, regulatory hurdles, patent updates, and market dynamics for the management of ophthalmic diseases that are available at the start of 2026 [16].

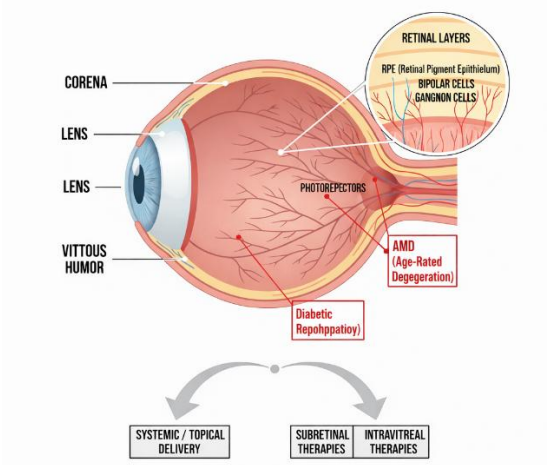


Figure 1. Schematic illustration of ocular anatomy and retinal layers showing major pathological sites in retinal disorders and common therapeutic delivery routes, including topical/systemic, subretinal, and intravitreal administration.

2. Research Gap

Although there have been significant strides in ophthalmic pharmacotherapy over the last 20 years, significant unmet needs and gaps in knowledge exist for retinal and optic nerve diseases [17]. Challenges are adherence to treatment, neuroprotection, geographic atrophy, safety of gene therapy, AI-driven personalization, and posterior-segment drug delivery.

2.1 Adherence to treatment and burden

Neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) typically require multiple intravitreal anti-VEGF injections. Evidence from the real world shows that there is a significant adherence issue. 45.9% of nAMD patients and 51.7% of DME patients said they felt overwhelmed with the frequency of treatment, and around one-third of the DME patients reported spending two to four hours in the clinic [18,19]. Data from 254,655 eyes within the IRIS Registry also support the decrease in treatment intensity, with 5.6 injections in year 2, and then around 4.2–4.6 injections per year between years 3 and 6. Furthermore, 38.8% of the patients dropped the treatment altogether [20]. Therefore, actual visual results are poorer than those found in clinical trials, as patients have lost a net 4.6 ETDRS letters by year 6 [21].

The treatment burden is multi-dimensional and comprises economic, logistical, psychological and geographical dimensions [24]. Factors that disproportionately impact elderly, rural and economically disadvantaged populations include injection cost, transportation, wait time, treatment anxiety and lack of access to retina specialists. The use of sustained-release products like the ranibizumab port delivery system (PDS) and the new AAV-based gene therapies will require fewer injections, but there are currently no validated markers to identify patients who are likely to respond to these therapies. [22,23]

2.2 Neuroprotection in Glaucoma

Although there are indications that glaucoma can progress without IOP reduction, IOP reduction is still the only proven pharmacological approach to glaucoma. Some patients, however, have IOP less than 21 mmHg at diagnosis and others progress despite a significant reduction in IOP [25]. Some of the other mechanisms, which are independent of IOP, are also important such as impaired autophagy, oxidative stress, glutamate excitotoxicity, mitochondrial dysfunction, and neuroinflammation [26].

Unfortunately, clinical translation of neuroprotective therapies so far has been disappointing. A large Phase 3 trial of memantine did not show evidence of visual-field progression [27]. Several investigational drugs have demonstrated promising preclinical or early clinical results for use in protecting the retina against glaucoma, such as nicotinamide, citicoline, coenzyme Q10, pyruvate, and GLP-1 receptor agonists, although none is approved by the FDA specifically for glaucoma neuroprotection [28–33]. There is still a long way to go for the development of validated biomarkers to detect the predominant metabolic or mechanical injury, to establish the optimal retinal delivery method and to provide evidence for when to initiate a neuroprotective intervention.

2.3 Dry AMD and Geographic Atrophy

Until recently there was no FDA-approved drug treatment for a late stage of atrophic AMD referred to as geographic atrophy or GA. In 2023, pegcetacoplan was approved and a year later, avacincaptad pegol, representing a new approach to complement inhibition, was approved.In 2023, complement inhibition received its first approvals with the approval of pegcetacoplan and that of avacincaptad pegol a year later. However, their clinical action is not that pronounced. Monthly doses of pegcetacoplan decreased the growth of GA lesions about 22% at 24 months, and every-other-month doses of avacincaptad pegol decreased growth about 27% at 12 months [38,39]. These effects slow down the growth of the lesions, but can not repair damage that has already occurred in the retina.

There are also safety concerns with complement inhibition, including a risk of worsening to neovascular AMD and intraocular inflammation [40]. Moreover, the monthly or bi-monthly injections could create the same adherence problem as anti-VEGF medications [41,42]. Thus, more work needs to be done to develop treatments that can prevent or slow the deterioration of retinal function, and not just the physical changes.

2.4 Gene Therapy Safety and Durability

Sustained intraocular transgene expression has the potential to decrease the frequency of treatment with AAV-based gene therapy. There are however important questions that still need to be addressed related to pre-existing neutralizing antibodies, inflammatory responses, long-term expression and the ability to administer again [43,44]. There may be major intraocular inflammatory complications and the long-term efficacy of therapeutic expression beyond five years is not yet known. The possibility of long-term safety monitoring has also been proposed due to potential AAV integration events [45]. One of the greatest unmet needs is the ability to develop predictive biomarkers that incorporate antibody status, immune-response characteristics, retinal morphology, and OCT-derived RPE integrity to identify those patients who are most likely to experience long-lasting benefits [19,46].

2.5 AI and Personalized Ophthalmic Medicine

AI systems have been highly effective in the diagnosis of DR, glaucoma, and AMD, with some systems achieving sensitivity of >90% in DR and AUC scores >0.95 in some DR applications; and >0.90 in some applications of glaucoma [47,48]. However, good diagnostic accuracy has not always been associated with better clinical results. Regulatory uncertainty, reimbursement restrictions, poor EHR interoperability, algorithmic bias, and lack of prospective validation are all barriers to adoption [49–52].

Demographic data, OCT and OCT-angiography biomarkers, genetic data, and previous treatment outcomes could also be used for personalized anti-VEGF treatment intervals with the help of AI [53-56]. Initial research indicates that possibly fewer injections can be provided and still achieve visual results. But, there is still no system that has proven its prospective evidence in routine clinical use with AI-based treatment interval recommendations. The issues of regulatory classification, clinical liability, explainability, and physician trust are still unaddressed [57,58].

2.6 Drug Delivery Across the Blood-Retinal Barrier

The blood-retinal barrier continues to be a significant barrier to non-invasive therapy of posterior-segment diseases. The bioavailability of the drug in the retina is extremely low when given topically due to the drainage of tears, the presence of barriers in the cornea, drug dilution and drug sequestration [59,60]. Intravitreal injection, although effective, is invasive and can also be associated with endophthalmitis and/or retinal detachment, and systemic administration is also inefficient.

New techniques involve the use of suprachoroidal delivery, iontophoresis, nanoparticles, and focused ultrasound. Most are still in the developmental phase, though, and a few delivery platforms have not proven to be effective in clinical trials [23]. Thus, the availability of a safe, reliable, and non-invasive device that could be used to achieve therapeutic levels in the posterior segment is one of the greatest unmet needs in ophthalmic pharmacology [62].

In general, there is a need for long-lasting therapies, validated predictive biomarkers, personalized treatment approaches, safe gene delivery methods, validated AI to be used in clinical practice, and non-invasive posterior-segment drug delivery in future ophthalmic research. Addressing these gaps may significantly lower treatment burden and enhance long-term visual outcomes and patient access to treatment.

3. Pathogenesis

3.1 Age-Related Macular Degeneration (AMD)

In older individuals, especially those over 60, a progressive multifactorial neurodegenerative disease affecting the central retina, age-related macular degeneration (AMD) is a dominant cause of irreversible central vision loss. It is characterized by the main involvement of the dysfunction of the retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaris, which constitute an important metabolic and nutritional unit for the photoreceptors[64]. The RPE has important roles including the phagocytosis of the outer segment of the photoreceptor, vitamin A recycling, and the maintenance of the outer blood-retinal barrier. Phagocytes, however, are very susceptible to oxidative damage because they are exposed to light, high concentration of oxygen, and ongoing phagocytosis throughout their life.

As cells grow older, the lysosomes of RPE cells deteriorate and accumulate the lipofuscin, especially bisretinoid A2E. This buildup disrupts the function of the lysosomes and has been known to produce reactive oxygen species under light conditions. Oxidative stress can impair mitochondrial DNA, membrane lipids, proteins and nucleic acids. Mitochondrial dysfunction then leads to decreased ATP formation and to the activation of apoptotic pathways. The lack of antioxidants again amplifies the effects of oxidative damage and plays a role in the onset and development of AMD[66].

Drukenstein is one of the hallmark early structural changes seen in AMD. These extracellular aggregates are formed between the basal lamina of the RPE and Bruch's membrane and consist of oxidized lipids, complement proteins, amyloid-β, vitronectin and incompletely degraded RPE material[68]. Drusen formation is associated with impaired clearance of cellular waste products, and with age-related changes in Bruch's membrane. Lipid deposition and thickening of Bruch's membrane decreases oxygen and nutrient delivery to the outer retina, and this chronic stress is thought to be a factor in the disease process.

Dysfunction of the complement system is also a key factor in AMD. Failure of the alternative complement pathway to be regulated may be due to genetic susceptibility, especially with regards to complement factor H. When activated, complement leads to the deposition of membrane attack complexes and to the release of inflammatory mediators. These processes are able to activate the NLRP3 inflammasome and stimulate inflammatory cytokines production. Activated microglia and macrophages migrate to the subretinal space and this leads to continuous inflammatory, oxidative, complement activation and RPE dysfunction[70].

These mechanisms lead to two big advanced stages of AMD. An additional phenomenon of RPE cell death occurs in geographic atrophy, where mitochondrial dysfunction and inflammatory injury are also observed, along with secondary photoreceptor loss. Loss of Choriocapillaris is an additional cause of retinal ischemia. Neovascular AMD is characterised by a disturbance of the proangiogenic/antiangiogenic balance caused by ischemia and inflammatory signalling, which increases VEGF-A levels and reduces PEDF levels. This causes the development of choroidal neovascularization across Bruch's membrane, which allows fluid to leak, bleed and eventually scar. Environmental factors, like smoking, are linked with genetic factors under investigation that include lipid metabolism, extracellular matrix remodeling, and cellular stress responses, which are all linked to the progression of disease[72].

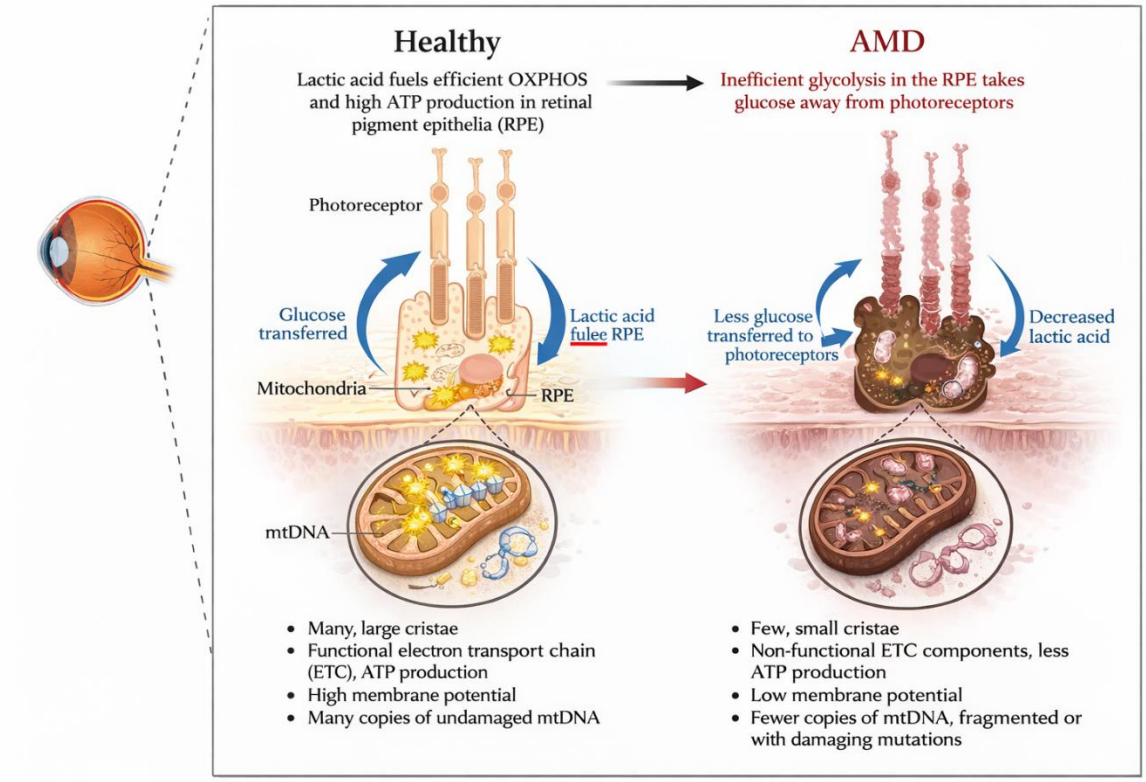


Figure 2. *Metabolic coupling between photoreceptors and retinal pigment epithelium (RPE) in health and age-related macular degeneration (AMD).*

3.2 Diabetic Retinopathy (DR)

Diabetic retinopathy is the most frequent microvascular diabetics complication and an important cause of preventable blindness in working age adults. Several mutually related biochemical pathways are responsible for the biochemical effect of chronic hyperglycemia on retinal vascular and neural tissues[74]. Four pathways are involved, the polyol pathway, the protein kinase C pathway, the hexosamine pathway, and the formation of advanced glycation end-products.

The polyol pathway is used to convert excess glucose to sorbitol, and uses NADPH and decreases the supply of antioxidants (such as glutathione). This leads to more oxidative and osmotic stress in pericyte and endothelial cells of the retina. Excess glucose also enhances the production of diacylglycerol, which activates protein kinase C, which in turn causes alterations in regulation of blood-flow in the retina, up-regulation of expression of vascular endothelial growth factor (VEGF), activation of inflammatory signaling pathways, and vascular leakage and vessel abnormalities[75].

The hexosamine pathway influences cellular proteins via O-linked glycosylation and inflammatory and profibrotic gene expression. However, glycation by non-enzymatic mechanisms generates AGE, which change the proteins of the basement membrane, reduce the activity of NO, and activate the receptors for AGEs. These processes activate inflammatory and oxidative pathways. Hyperglycemia, taken together, leads to augmentation of mitochondrial production of superoxide and creates a vicious circle of glucotoxicity and retinal damage.

DR is currently considered a vascular and neurodegenerative disease. Neuronal dysfunction of the retina, such as ganglion cell damage, amacrine cell damage, and Müller glia injury, can happen in the absence of apparent vascular changes[76]. Hyperglycemia may lead to glutamate excitotoxicity, mitochondrial impairment and defective insulin and IGF-1 signaling for neuroprotective function. During metabolic stress, Müller cells undergo reactive gliosis and secrete inflammatory cytokines and VEGF, which exacerbate further neuronal and vascular damage.

3.3 Glaucoma

Glaucoma is a spectrum of optic neuropathies that all share the common features of progressive optic-nerve ganglion cell and axon degeneration, optic-nerve-head structural damage, and visual-field loss, all of which are irreversible. The primary types of glaucoma are primary open-angle glaucoma, primary angle-closure glaucoma, normal-tension glaucoma and secondary glaucomas. While their triggers are different, all of them end up in apoptosis of retinal ganglion cells.

An increase in the pressure of eye fluids (aqueous humor) is common in primary open-angle glaucoma and occurs because the aqueous humour is not draining from the eye due to increased resistance through the trabecular meshwork and Schlemm's canal[77]. Outflow facility decreases as a result of the accumulation and remodeling of the components of the extracellular matrix in the trabecular meshwork. These changes are mediated in part by transformation growth factor-β2, which causes tissue stiffening, changes in matrix metalloproteinase activity and elevations in connective tissue growth factor. Increased intraocular pressure is transferred to the lamina cribrosa causing mechanical stress and distortion of the retinal ganglion cell axons. This may disrupt the transport of neurotrophic factors in the axoplasm and help to trigger progressive damage to the neurons.

Vascular mechanisms are more prominent in normal-tension glaucoma. The ocular perfusion pressure is the difference between systemic arterial pressure and intraocular pressure. Optic nerve head ischemia can be caused by the reduction of blood flow due to systemic hypotension, nocturnal reduction of blood pressure, vasospasm or other vascular abnormalities[78]. Mitochondrial ROS generation and lipid peroxidation are increased in ischemia-reperfusion injury. Endothelin-1 also can further impair blood flow in the optic nerve head and help cause retinal ganglion cell damage.

3.4 Dry eye disease (DED)

Dry eye disease is a chronic, multifactorial condition in which the tear-film homeostasis is impaired and the ocular surface is damaged. It may be due to insufficient tear production or to increased tear evaporation, which is often related to dysfunction of the meibomian gland. However, whatever is the cause of the tear film hyperosmolarity is a major initiating factor[78].

The stress pathways activated in the intracellular environment include MAPK, NF-κB, and NLRP3 inflammasome signaling in the epithelial cells of the ocular surface in the presence of hyperosmolarity. This leads to production of inflammatory mediators like IL-1β, TNF-α and IL-6. These mediators attract immune cells, such as Th1 and Th17 lymphocytes, which secrete their own inflammatory cytokines[79]. The inflammation that follows leads to epithelial apoptosis, breakdown of tight junctions and increased activity of matrix metalloproteinases. Loss of goblet cells and decrease of MUC5AC secretion further compromise the tear film.

3.5 Cataract

Cataract is the cloudiness of the crystalline lens that is severe enough to interfere with vision, and the most common cause of reversible blindness in the world. The structural organization and stability of crystallin proteins, especially α-, β-, and γ-crystallins, is important to the transparency of the lens. α-crystallin acts as a molecular chaperone and to prevent aggregation of damaged proteins in the lens.

Oxidative stress and reduced antioxidant protection are highly linked with age-related cataract. Glutathione, superoxide dismutase, catalase, and other antioxidant systems are normally present in the lens and keep it in a reduced state[77]. Ageing causes a decrease in concentration of reducing glutathione, which results in oxidative modifications of crystallins, such as methionine oxidation, disulfide formation, carbonylation, deamidation, and glycation. These alterations disrupt crystallin proteins and lead to the formation of aggregates of high molecular weight which scatter light. The chaperone activity of α-crystallin also decreases with age, and protein aggregation and loss of transparency occur[80].

3.6 Uveitis

Uveitis is an inflammation of the uveal tract (iris, ciliary body and choroid). Uveitis can be categorized as anterior, intermediate or posterior, depending on the main location of the disease. In panuveitis, all parts of the eye are inflamed. The most common type is anterior uveitis. If inflammation does not abate, or comes back, serious complications may occur such as cataract, glaucoma, macular edema, retinal damage, and vision loss[81].

Uveitis is associated with inflammatory process which damages the normal blood-ocular barrier, permitting inflammatory cells or mediators to invade the eye's tissues. It may cause changes in the iris, ciliary body, vitreous, retina and/or choroid, depending on the anatomical structures involved[82]. Continued inflammation can affect

normal retinal and vascular function and result in secondary structural damage. Macular edema is a significant cause for loss of vision associated with chronic inflammatory eye disease.

4. Classification of Ophthalmic Disease

The major ophthalmic diseases classified by anatomical compartment, etiological basis and stage of severity are below: (https://www.nei.nih.gov/eye-health-information/eye-conditions-and-diseases, NIH)

Table 3. *Classification and staging of major ophthalmic diseases, summarizing disease types, hallmark clinical features, and severity grading systems used in current clinical practice.*

Disease	Type/Category	Key Features	Severity Stage
Glaucoma	Primary Open-Angle (POAG)	Elevated IOP, RGC loss, cupping	Mild → Moderate → Severe → End-stage
	Angle-Closure Glaucoma	Acute IOP spike, anterior chamber shallowing	Acute, Subacute, Chronic
AMD	Dry (Atrophic)	Drusen, RPE atrophy, geographic atrophy	Early → Intermediate → Advanced (GA)
	Wet (Neovascular)	CNV, subretinal fluid, rapid vision loss	Active CNV, Scarring, Disciform
Diabetic Retinopathy	Non-Proliferative (NPDR)	Microaneurysms, hemorrhages, hard exudates	Mild → Moderate → Severe NPDR
	Proliferative (PDR)	NVD/NVE, vitreous hemorrhage, TRD	Early PDR → High-Risk PDR → Advanced
Dry Eye Disease	Aqueous Deficient	Low Schirmer score, reduced tear secretion	TFOS DEWS II Mild/Moderate/Severe
	Evaporative	Meibomian gland dysfunction, high osmolarity	Grade 1–4 (MGD grading)
Cataract	Nuclear / Cortical / PSC	Lens opacity, reduced visual acuity	LOCS III Grade 1–5
Uveitis	Anterior / Posterior / Panuveitis	Intraocular inflammation, cells/flare, CME	Active / Inactive / Recurrent

5. Conventional Methodology for Disease Management

5.1 Diabetic Retinopathy and Diabetic Macular Edema

Diabetic retinopathy (DR) management is dependent upon disease severity and aims to prevent disease progression and vision threatening complications. Systemic control of risk factors, notably intensive glycaemic and blood pressure control is the first step. There has been evidence that strict glycemic control (HbA1c < 7%) can significantly prevent and slow the onset of diabetic retinopathy[85]. Diabetes-related eye disease including retinal lesions, diabetic macular edema (DME), capillary non-perfusion and neovascularization can be detected in early stages with regular ophthalmic monitoring using dilated fundus exam, ultra-widefield photography, spectral-domain OCT and fluorescein angiography.

PRP is still a recognized treatment for high risk P.D.R. It decreases ischemic retinal tissue, and thereby the amount of VEGF-induced neovascularization, thus reducing the risk of vitreous hemorrhage and tractional retinal detachment. Intravitreal anti-VEGF therapy has largely replaced conventional focal and grid laser photocoagulation for center-involving DME, due to the improved visual outcomes. These medications are often administered via loading doses and then as treat and extend (T&E) or treat as needed (TAK) treatments[86].

Intravitreal corticosteroid implants could be used in patients who are poorly responsive to anti-VEGF therapy, especially in pseudophakic or vitrectomized eyes. Dexamethasone and fluocinolone acetonide implants can last a long time, but can also lead to an increased risk of cataract and elevated intraocular pressure[87]. Pars plana vitrectomy is only indicated for severe complications like persistent vitreous hemorrhage, tractional retinal detachment with or at risk of involving the macula, epiretinal membrane (ERM) and selected cases of refractory DME with vitreoretinal traction.

5.2 Age-Related Macular Degeneration

Treatment for age-related macular degeneration (AMD) hinges largely on whether it is dry or neovascular. For appropriate patients with early or intermediate AMD, the AREDS2 nutritional supplementation with vitamin C, vitamin E, lutein, zeaxanthin, zinc and copper may slow down the progression to advanced AMD[87]. But supplements won't repair harm already done to the retina. For geographic atrophy, complement inhibitors like pegcetacoplan and avacincaptad pegol can slow the progression of lesions, but they cannot improve vision loss.

Intravitreal anti-VEGF therapy is the recommended therapy for neovascular AMD. These agents are ranibizumab, aflibercept, bevacizumab, brolucizumab and faricimab. The treatment schedules can include loading doses and/or treat-and-extend treatments for disease control and to decrease treatment frequency. Photodynamic therapy with verteporfin continues to have a place in certain patients, such as polypoidal choroidal vasculopathy, where a combination therapy may help to promote polyp regression. Low vision rehabilitation, magnification devices,

eccentric-viewing training and adaptive technologies can be useful for patients with irreversible loss of vision who cannot be corrected.

5.3 Glaucoma

The primary goal when managing glaucoma is to decrease intraocular pressure (IOP), which is the single most important modifiable risk factor that has been shown to slow retinal ganglion cell loss and visual-field progression. Prostaglandin analogues such as latanoprost, bimatoprost and travoprost are frequently used as first-line treatment, as they are effective at significantly reducing IOP with only a single dose per day[85]. Other drugs used are alpha-2 adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, and rho kinase inhibitors. If a monotherapic drug is not able to produce the desired target IOP then combination therapy is used. Oral acetazolamide is rarely used for acute pressure elevation, or as a temporary solution prior to surgery.

Selective laser trabeculoplasty (SLT) is an important alternative to topical medication, and is used to remodel the trabecular meshwork to increase aqueous outflow. If the medical or laser treatment is not effective enough in controlling the IOP, surgery might be necessary. These can be minimally invasive glaucoma surgery (MIGS), trabeculectomy, or a glaucoma drainage device. Neuroprotective treatments that target IOP independent mechanisms are still being studied and do not have approved pharmaceutical therapy at this time[86].

5.4 Dry Eye Disease

The treatment of dry eye disease (DED) proceeds step-wise, depending on the severity of the disease and is designed to improve symptoms and treat tear-film instability, hyperosmolarity and inflammation of the ocular surface. Artificial tears containing sodium hyaluronate, carboxymethylcellulose, polyethylene glycol or hydroxypropyl methylcellulose are often prescribed as first-line treatment. Preservative-free preparations are more desirable when frequent use is planned in order to decrease the risk of preservative-induced ocular-surface toxicity with prolonged use.

For moderate to severe inflammatory DED, topical cyclosporine or lifitegrast might be used to treat the condition, which is an immunomodulatory therapy[87]. These agents can decrease inflammation in the eye caused by T cells, and enhance the stability of the eye surface. Punctal plugs may help preserve tears against drainage, might be especially helpful in aqueous deficient dry eye. They would, however, not be appropriate in cases where there are significant meibomian gland dysfunctions as inflammatory substances may be left on the ocular surface.

Meibomian gland dysfunction is a management component of evaporative DED and involves using warm compresses and lid hygiene regularly. Other therapies, like intense pulsed light and thermal pulsation therapy, can help enhance meibomian gland function by decreasing lipid obstruction and enhancing the lipid layer in the tear film. Therefore, standard treatment involves tear replacement, treatment of inflammation, tear conservation and treatment of underlying eyelid and meibomian gland problems.

6. Drugs Related to Ophthalmic Disease (conventional Pharmacotherapy)

The following table summarizes conventional pharmacological agents used in the management of ophthalmic disease with their mechanism of action, primary indications, and dosing routes [137]

Table 4. *Currently approved pharmacologic therapies in retinal and ocular diseases, detailing drug class/mechanism of action, clinical indications, and standard routes and dosing frequencies.*

Drug Name	Brand	Class/MOA	Indication	Route/Freq.
Ranibizumab	Lucentis	Anti-VEGF Fab fragment	nAMD, DME, BRVO/CRVO	Intravitreal q4w
Aflibercept 2mg	Eylea	VEGF trap fusion protein	nAMD, DME, DR	IVT q4-8w
Aflibercept 8mg	Eylea HD	High-dose VEGF trap	nAMD, DME, DR	IVT q12-16w
Faricimab	Vabysmo	Bispecific anti-VEGF/Ang-2	nAMD, DME	IVT q4-16w (TAE)
Brolucizumab	Beovu	Single-chain anti-VEGF	nAMD, DME	IVT q12w
Bevacizumab	Avastin	Anti-VEGF mAb (off-label)	nAMD, DME, PDR	IVT q4-6w
Pegcetacoplan	Syfovre	Complement C3 inhibitor	Geographic atrophy	IVT q1m or q2m
Avacincaptad pegol	Izervay	Complement C5 inhibitor	Geographic atrophy	IVT q1m
Latanoprost	Xalatan	PGF2α analogue (IOP↓)	Glaucoma / OHT	Topical once daily
Timolol	Timoptic	β-blocker (aqueous↓)	Glaucoma / OHT	Topical 0.25-0.5% BD
Brimonidine	Alphagan	α2-agonist (IOP↓)	Glaucoma, neuroprotection	Topical 0.1-0.15% TDS

Cyclosporine 0.05%	Restasis	Immunomodulator (T-cell↓)	Dry eye disease	Topical BD
Lifitegrast 5%	Xiidra	LFA-1 antagonist (anti-inflam)	Dry eye disease	Topical BD
Teprotumumab	Tepezza	IGF-1R inhibitor	Thyroid Eye Disease	IV q3w x 8 doses
Dexamethasone implant	Ozurdex	Corticosteroid biodegradable	DME, RVO, uveitis	IVT q3-6m

Anti-VEGF agents collectively constitute the dominant pharmacological class, accounting for 38.1% of the global ophthalmic drug market by therapeutic class in 2023. In 2024, the monoclonal antibodies and fusion proteins segment accounted for 84.3% of the ophthalmology drugs market, attributed to the proven efficacy of aflibercept, faricimab, ranibizumab, and brolucizumab in retinal vascular diseases.

7. New Technology and Drugs Related to Ophthalmic Disease

7.1 Gene Therapy Platform

Recent technological development of gene therapy is an important advance in ophthalmology, especially in the treatment of inherited retinal disorders and chronic retinal diseases. A breakthrough was used for the approval of voretigene neparvovec-rzyl (Luxturna) for RPE65 mutation-associated Leber congenital amaurosis in 2017. Luxturna is delivered via subretinal injection of an adeno-associated virus type 2 (AAV2) vector that carries an active RPE65 gene. These factors make the eye an ideal target for gene therapy: it is small; accessible; relatively immune privileged[142].

Currently, gene therapy is being studied for acquired retinal conditions such as the neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME). The goal is to maintain the production of therapeutic proteins in the eye and, consequently, avoid the need for repetitive intravitreal injections. One of the most advanced therapies is based on AAVs. The clinical development programs currently underway are: 4D-150, ixoberogene soroparvovec (Ixo-vec) and ABBV-RGX-314. These therapies have various viral capsids, transgenes, and delivery methods that yield long-term anti-VEGF activity[143].

A new technique is called RNA editing with CRISPR. The CRISPR/Cas13 system developed into HG202 is an RNA targeting approach to the treatment of wet AMD. In contrast to Cas9, that changes the DNA, the Cas13 will recognize specific RNA transcripts without changing the genetic sequence in the genome. This may provide a potentially safer and more reversible method of regulating VEGF-related signaling.

7.2 Sustained-Release Drug Delivery Systems

Intravitreal injections are one of the biggest challenges for treatment of chronic retinal conditions like nAMD, DME and DR. The number of injections patients may need to have annually can be significant, adding to treatment burden and potentially to non-adherence and undertreatment. To achieve this, sustained release systems for drug delivery have been developed to provide a therapeutic level of a drug over an extended period following the initial dose or infrequent refill[144].

The Susvimo Port Delivery System is an advanced sustained-release platform. It is a reusable intraocular reservoir made to deliver a constant dose of ranibizumab, which is inserted through the pars plana. The system is designed to provide a level of drug with no repeated "peaks and troughs" as found in conventional injection. Other technologies are a biodegradable PLGA hydrogel implant containing axitinib (OTX-TKI/AXPAXLI), which aims to produce long-lasting anti-VEGF receptor activity. Fluocinolone acetonide implants offer prolonged chronic DME therapy with corticosteroid delivery and may be especially beneficial in certain anti-VEGF treatment-refractory or pseudophakic patients[145].

Anterior-segment diseases also are the subject of sustained-release systems. Intracameral bimatoprost implants may be more effective in reducing the IOP over time in glaucoma patients than daily eye drops, potentially increasing the likelihood of compliance[144]. Nanoparticle gels, in-situ gelling systems, drug-eluting contact lenses and punctal plugs may help increase the duration of the drugs on the ocular surface in the eyes of patients with dry eye disease and allergic conjunctivitis. The overall goal of these systems is to optimise the pharmacokinetics, lower the dosage frequency and increase treatment compliance.

7.3 Novel Pharmacological Agents

The new era in ophthalmology is about to move beyond the use of anti-VEGF agents and steroids, and instead focus on specific molecular and cellular pathways. For example, acoltremon ophthalmic solution, a TRPV1 receptor agonist for dry eye disease. Unlike replacement tears and anti-inflammatory medications, it does not just replace tears or anti-inflammatory, it stimulates the sensory nerves in the eye and stimulates the secretion of aqueous and mucin tears. This method is a solution to the neurosensory cause of dry eye[147].

Diabetic retinopathy and DME are treated increasingly with newer therapies that target multiple pathways, which result in vascular leakage and inflammation. Combined VEGF/angiopoietin-2 inhibition may enhance vascular stability and potentially decrease the number of injections. Other promising strategies are being explored such as plasma kallikrein inhibitors, integrin antagonists and gene therapies for continuous anti-VEGF expression. Complement inhibitors targeting C3 and C5 offer options of treatment for AMD that target the inflammatory processes involved in geographic atrophy[148].

Glaucoma therapy has also evolved, with Rho-kinase inhibitors, which are able to change the cytoskeletal activity to improve trabecular outflow. In addition to lowering IOPs, new therapies targeting the NMDA receptors and mitochondrial dysfunction are being studied that could protect retinal ganglion cells without lowering IOP. Newer immunomodulatory agents, new formulations of cyclosporine, biologic tear substitutes, regenerating peptides and nerve-growth-factor based treatments are under investigation for their ability to restore ocular surface homeostasis in dry eye disease.

7.4 Nanotechnology-Based Drug Delivery

The innovative nature of nanotechnology opens opportunities to overcome anatomical and physiological resistance to drug delivery in the eye. There are many factors that can decrease the amount of medication that reaches the target, such as corneal epithelium, blood-retinal barrier, vitreous, and rapid precorneal drug clearance[148]. Nano particles can be used to enhance the stability, penetration, retention, and controlled release of a drug.

The delivery of mRNA, siRNA and other nucleic acids are being evaluated using lipid nanoparticles. They can make it easier to deliver genes into cells and offer an alternative to AAV gene therapy. Polymeric nanoparticles, which can be prepared of materials like PLGA and PLA, can be used to control drug delivery and surface modifications can enhance the penetration and retention of the drug in the eye. Several other types of nanocarriers have been explored for anti-inflammatory, anti-angiogenic and retinal protection therapies[149].

7.5 AI and Digital Diagnostics

The eye diseases produce vast amounts of image based information that makes artificial intelligence (AI) an important part of ophthalmic diagnostics. A deep-learning system, especially a convolutional neural network, can be used to detect and classify disease by analyzing retinal photographs and OCT images. AI-based DR screening has been shown to have high diagnostic accuracy and facilitated automated screening methods capable of being applied in primary care in a DR screening setting.

Another method AI is used in AMD is to look at imaging features of the retina that are linked to progression to neovascular AMD. Automated OCT analysis can quantify features like drusen, hyperreflective foci, outer retinal abnormalities and intra- or subretinal fluid. These measurements can aid in making individualized treatment decisions and optimizing anti-VEGF treatment intervals[152].

AI-powered telemedicine and home-monitoring tools can help in glaucoma to recognize IOP patterns that might go unnoticed during traditional in-clinic exams. AI is also being explored in surgery, such as in retinal membrane peeling and subretinal delivery procedures. These technologies have the potential to enhance precision and enable more effective delivery of cutting-edge and advanced therapies, including gene therapies.

8. Advantages and Disadvantages of Conventional Vs. Emerging Technologies

The table below systematically compares the therapeutic approaches, highlighting clinical trade-offs that inform treatment selection and drive ongoing innovation: [195,196]

Table 5. *Comparative overview of conventional and emerging therapeutic approaches in ophthalmology, highlighting key technologies, clinical advantages, and current limitations affecting long-term efficacy, safety, cost, and patient adherence.*

Approach	Drug/Technology	Advantages	Disadvantages / Limitations
Anti-VEGF Injections (Conventional)	Ranibizumab, Aflibercept, Bevacizumab	Proven efficacy; reversible vision loss; multiple FDA approvals; monthly/bimonthly flexibility	Frequent injections; patient burden; endophthalmitis risk; non-adherence; high cost (~$1,850-2,000/dose)
Bispecific mAb (Faricimab)	Vabysmo (Ang-2 + VEGF-A)	Dual pathway blockade; extended intervals (up to 16w); reduces treatment burden	Limited long-term real-world data; higher cost; narrow approved intervals
Complement Inhibitors (Dry AMD)	Pegcetacoplan, Avacincaptad pegol	First-ever pharmacotherapy for GA; slows lesion growth; monthly or bimonthly dosing	Modest effect size; risk of converting to wet AMD; injection burden unchanged
Laser Photocoagulation	PRP (panretinal); Focal/grid	Durable effect; low-cost; widely available; reduces neovascularization	Permanent retinal damage; peripheral field loss; painful; cannot treat macula
Topical IOP-Lowering Therapy	Latanoprost, Timolol, Brimonidine, Dorzolamide	Convenient; effective IOP reduction; wide spectrum of options; generic availability	Daily adherence required; systemic absorption; conjunctival hyperemia;

			corneal toxicity from preservatives
Gene Therapy (AAV-based)	4D-150, RGX-314, Luxturna	Single administration; sustained expression; eliminates injection burden; potentially curative	Immune response to vector; inflammation; high manufacturing cost; Phase 3 data pending; no reversal
Sustained-Release Implants	Susvimo, Ozurdex, Iluvien	Reduced injection frequency; steady drug levels; improved compliance	Surgical insertion; conjunctival erosion risk; refill procedures; explant if complications
Topical Dry Eye Therapy	Cyclosporine, Lifitegrast, Acoltremon	Non-invasive; immunomodulatory; symptom and sign improvement; FDA approved	Slow onset (3-6 months); burning/stinging sensation; cost; patient non-compliance
Nanoparticle Delivery	LNPs, dendrimers, liposomes	Enhanced bioavailability; targeted delivery; penetrates BRB; sustained release	Regulatory complexity; immunogenicity concerns; stability issues; mostly preclinical stage

9. Barrier Affecting Ophthalmic Disease Management

Effective management of ophthalmic diseases is impeded by a hierarchical set of barriers spanning anatomy, physiology, immunology, patient access, and regulatory science: (197–199)

9.1 Anatomical barrier in detail

The eye is uniquely compartmentalized, creating distinct pharmacokinetic challenges for each anatomical segment. The corneal epithelium presents a formidable barrier with tight junctions restricting paracellular transport; only lipophilic, low-molecular-weight compounds penetrate effectively. [200] The blood-retinal barrier (BRB) — comprising inner BRB (retinal vascular endothelial tight junctions via ZO-1, occludin, claudin-5) and outer BRB (RPE tight junctions) — prevents systemic drug access to the retina with extraordinary selectivity.[201] Intravitreal injection circumvents the outer barriers but introduces its own pharmacokinetic limitations: vitreous diffusion is size-dependent, with large biologics exhibiting limited diffusion from the injection site to the retinal surface.[202]

9.2 Patient-Level and Systemic Barriers

Non-adherence to anti-VEGF treatment protocols is perhaps the most clinically impactful barrier. Studies demonstrate that 40–50% of real-world patients fail to adhere to recommended injection schedules, driven by injection anxiety, travel difficulty (particularly for elderly patients), financial cost ($1,850–2,000 per aflibercept injection; $14,000–23,500 per year), systemic comorbidities, and lack of perceived benefit after initial stabilization. These barriers disproportionately affect patients in low- and middle-income countries (LMICs), where diagnostic infrastructure, trained ophthalmologists, and healthcare financing are severely limited.[203]

10 Novel Ocular Drug Delivery, Recent Patents, Market Overview and Future Trends

Advanced ocular drug delivery technologies are also being developed to overcome the anatomical barriers of the eye, and to enhance drug bioavailability, increase the duration of drug delivery, and decrease dosing frequency[203]. Eye drops do not penetrate the eye sufficiently and repeated intravitreal injection may lead to a heavy burden of treatment and procedural risks. Hence, more and more formulations today involve a targeted, sustained and non-invasive manner in which the drug is delivered.

Novel ocular drug-delivery systems include liposomes, lipid nanoparticles, hydrogels, microneedles, ocular inserts, drug-eluting contact lenses, dendrimers and mucoadhesive nanoparticles. Liposomes can contain both hydrophilic and hydrophobic drugs, which can help with the retention and controlled release of the drugs in the eye, but there are also some challenges to aggregate, stability and manufacturing costs[202]. The controlled delivery of drug-loaded solid lipid nanoparticles and nanostructured lipid carriers (NLCs) with enhanced bioavailability to the cornea are offered. NLCs have higher drug loading capacity. Hydrogels and in-situ gelling systems convert into gels following administration resulting in prolonged drug release and extended precorneal residence time.

Microneedles are a minimally invasive delivery method via corneal, transscleral, or suprachoroidal route, and may enhance posterior-segment targeting. Ocular inserts and drug-eluting contact lenses can provide continuous drug release while reducing dosing frequency. The use of dendrimers and mucoadhesive nanoparticles also increases retention in the eye and absorption of the drug due to its extended residence time in the ocular tissues[204]. The technologies are especially relevant in the context of glaucoma, dry eye disease (DED), uveitis, diabetic macular edema (DME), diabetic retinopathy (DR) and other retinal diseases and conditions.

The current patent landscape shows of the speedy innovation in the Ophthalmology field. Major focus areas of development during 2022-2024 include lipid nanoparticle delivery of mRNA and siRNA, CRISPR-based RNA editing, suprachoroidal delivery devices, hydrogel based sustained-release implants, and AI assisted retinal

imaging and advanced gene-therapy vectors. Key patent strategies encompass developing more efficient AAV capsids for retinal targeting, nucleic-acid delivery without viral vectors, bispecific antibody platforms, RNA editing and stimuli-responsive biomaterials and artificial intelligence for diagnosis and treatment planning. The progress made suggests a change to more targeted and potentially more effective and durable treatments rather than standard pharmacological therapy[202].

The ophthalmic pharmaceutical market is also a rapidly growing market. According to the source material, the global ophthalmic drugs market is expected to grow to USD 18.34–38.20 billion by 2024 and USD 26.28–62.08 billion by 2030. North America is emerging as the biggest market in the region due to favorable government regulations and reimbursement policies, along with robust research and development activities in the pharmaceutical industry. One of the fastest-growing areas is anticipated to be gene and cell therapies. The anti-VEGF therapies are still significant for the retinal area, and glaucoma and age-related diseases are still creating significant demand.

Eylea (aflibercept), Eylea HD, Vabysmo (faricimab), Beovu (brolucizumab), Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol) are all major commercial products used for treating retinal diseases[188]. The increasing significance of long-duration delivery is reflected in sustained-release products like Susvimo and Ozurdex. Continuing innovation in dry-eye treatments is demonstrated by Restasis, Xiidra and newer treatments like Tryptyr for ocular-surface dry-eye. Although not the only treatment option for glaucoma, Latanoprost is still a valuable treatment, and biosimilar ranibizumab products like Byooviz and Cimerli are providing competition and potentially making treatment more affordable.

One important aspect of the biosimilar landscape is that it could drive down the price of anti-VEGF therapy with more competition. Biosimilars of ranibizumab have already been launched in the market and the development of biosimilars of aflibercept is anticipated to further create competition[186]. This trend can make access to retinal therapies more convenient, especially in low and middle income countries where the price of therapy is often a significant constraint.

In conclusion, the treatment for ophthalmic diseases is shifting from multiple short-term treatments to long acting targeted (and to a great extent biologically based) treatment options. New innovations are transforming the management of ophthalmic disease, including gene therapy, sustained-release implants, lipid nanoparticles, CRISPR-based methods, complement inhibition, and regenerative medicine, along with AI-driven diagnostics. However, there are obstacles to overcome, such as adherence to treatment, development costs, regulatory complexity, availability of advanced treatment and the lack of validated biomarkers and effective neuroprotective strategies. Ongoing innovation is thus key to the successful preservation of the eye's vision and to minimizing the burden of treatment and maximizing treatment effectiveness for patients with major blinding disorders[198].

11. CONCLUSION

The treatment of eye diseases is moving away from repeatedly treating the symptoms toward long-lasting, biologic-based therapies. Advances in gene therapy, sustained-release drug delivery systems, complement inhibition, CRISPR-based editing and regenerative medicine are creating the possibility of long-lasting, or potentially curative, interventions for major blinding disorders. AAV vector engineering, lipid nanoparticles, iPSC-derived cell therapies and AI-assisted diagnostics have fast-tracked this transformation with milestones such as Phase 3 ocular gene therapy programs, CRISPR ocular trials and approvals of sustained-release implants.

However, there are still many major challenges, including low adherence to frequent treatment regimens, limited access to advanced care in low-resource settings, and the need for effective neuroprotective therapies and validated biomarkers for emerging nanotechnology-based platforms. However, the field is entering a new era of durable vision preservation and reduced treatment burden as the market for ophthalmic therapeutics is rapidly expanding and gene therapy is showing great promise in the clinic.

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